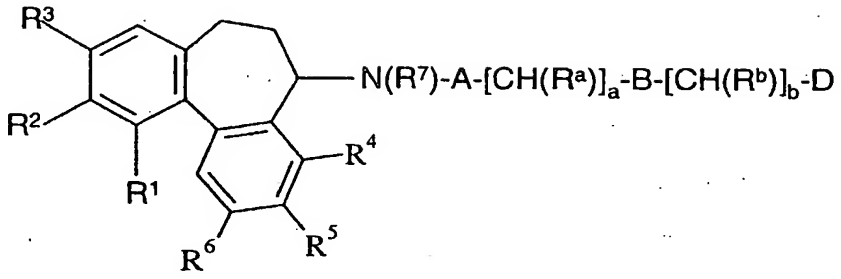
Claims

1. A compound of the formula (I):



(I)

wherein:

$\mathbb{R}^1$, $\mathbb{R}^2$ and $\mathbb{R}^3$ are each independently hydroxy, phosphoryloxy ($-OPO_3H_2$), C_{1-4}alkoxy or an in vivo hydrolysable ester of hydroxy, with the proviso that at least 2 of R^1, R^2 and R^3 are C_{1-4}alkoxy;

A is - CO-, -C(O)O-, $-CON(R^8)$-, $-SO_2$- or $-SO_2N(R^8)$- (wherein $\mathbb{R}^8$ is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, aminoC_{1-3}alkyl or hydroxyC_{1-3}alkyl);

a is an integer from 1 to 4 inclusive;

$\mathbb{R}^a$ and $\mathbb{R}^b$ are independently selected from hydrogen, hydroxy and amino;

B is -O-, -CO-, $-N(R^9)CO$-, $-CON(R^9)$ -, -C(O)O-, $-N(R^9)$ -, - $N(R^9)C(O)O$-, $-N(R^9)CON(R^{10})$-, $-N(R^9)SO_2$-, $-SO_2N(R^9)$- or a direct single bond (wherein $\mathbb{R}^9$ and $\mathbb{R}^{10}$ are independently selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, aminoC_{1-3}alkyl and hydroxyC_{1-3}alkyl);

b is 0 or an integer from 1 to 4 inclusive, (provided that when b is 0, B is a single direct bond);

D is carboxy, sulpho, tetrazolyl, imidazolyl, phosphoryloxy, hydroxy, amino, N-(C_{1-4}alkyl)amino, N,N-di(C_{1-3}alkyl)amino or of the formula $-Y^1-(CH_2)_cR^{11}$ or $-NHCH(R^{12})COOH$; [wherein Y^1 is a direct single bond, -O-, -C(O)-, $-N(R^{13})$-, $-N(R^{13})C(O)$- or $-C(O)N(R^{13})$- (wherein $\mathbb{R}^{13}$ is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, aminoC_{2-3}alkyl or hydroxyC_{2-3}alkyl); c is 0 or an integer from 1 to 4 inclusive; $\mathbb{R}^{11}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) containing 1 or 2 ring heteroatoms, selected independently from

O, S and N, or a 5-6-membered unsaturated or partially unsaturated heteroaryl group (linked via carbon or nitrogen) containing 1 or 2 ring heteroatoms, selected independently from O, S and N, which heterocyclic group or heteroaryl group may bear 1 or 2 substituents selected from:

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{2-4}alkanoyl, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-di-(C_{1-4}alkyl)carbamoyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, cyanoC_{1-3}alkyl, carbamoylC_{1-3}alkyl, carboxyC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, di-N,N-(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and R^{14} (wherein R^{14} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) containing 1 or 2 ring heteroatoms, selected independently from O, S and N, which heterocyclic group is optionally substituted by 1 or 2 substituents selected from:

oxo, hydroxy, halogeno, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

R^{12} is an amino acid side chain;

R^5 is C_{1-4}alkoxy;

R^4 and R^6 are each independently selected from: hydrogen, fluoro, nitro, amino, N-C_{1-4}alkylamino, N,N-di-(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy and C_{1-4}alkyl;

R^7 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, aminoC_{1-3}alkyl or hydroxyC_{1-3}alkyl;

or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

2. A compound according to claim 1 where R^1, R^2 and R^3 are all methoxy.
or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

3 A compound according to claim 1 wherein:

R^1 , R^2, and R^3 are all C_{1-4}alkoxy;

R^4 and R^6 are independently selected from hydrogen, hydroxy, C_{1-3} alkoxy, and C_{1-3}alkyl;

R^5 is methoxy;

A is -CO-, -C(O)O- or -CONH-;

a is 1, 2 or 3;

B is -CO-, -NHCO-, -CONH, -C(O)O-, -NH-, -NHC(O)O-, NHCONH- or a single direct bond;

b is 0, 1 or 2;

D is carboxy, sulpho, phosphoryloxy, hydroxy, amino, N-C_{1-4} alkylamino, N,N-di(C_{1-4} alkyl)amino or of the formula $-Y^1(CH_2)_cR^{11}$ (wherein Y^1 is -NHC(O)- or -C(O)NH-; c is 1 or 2; R^{11} is a 5-6-membered saturated heterocyclic group (linked via nitrogen) containing 1 or 2 ring heteroatoms, selected independently from O and N, which heterocyclic group may bear 1 or 2 substituents selected from:

C_{1-4} alkyl, C_{2-4}alkanoyl, carbamoyl, cyanoC_{1-3}alkyl, hydroxyC_{1-3}alkyl, carboxyC_{1-3}alkyl and aminoC_{1-3}alkyl);

R^7 is hydrogen;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

4. A compound according to claim 1 wherein:

R^1 , R^2, and R^3 are all methoxy;

R^4 and R^6 are independently selected from hydrogen, hydroxy, methoxy and methyl;

R^5 is methoxy;

A is -CO-, -C(O)O- or -CONH-;

a is 2 or 3;

B is -CO-, -NHCO-, -CONH or a single direct bond;

b is 0 or 1;

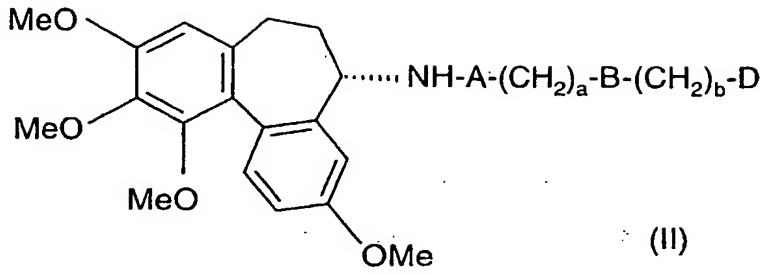
D is carboxy, phosphoryloxy, hydroxy, amino, N-C_{1-4} alkylamino, N,N-di(C_{1-4} alkyl)amino or of the formula $-Y^1(CH_2)_cR^{11}$ (wherein Y^1 is -NHC(O)- or -C(O)NH-; c is 1 or 2; R^{11} is piperazinyl, morpholinyl or piperidinyl, each of which is linked via a ring nitrogen atom and each ring is optionally substituted by 1 or 2 substituents selected from:

C_{1-4}alkyl, C_{2-4}alkanoyl, carbamoyl, cyanoC_{1-3}alkyl, hydroxyC_{1-3}alkyl, carboxyC_{1-3}alkyl and aminoC_{1-3}alkyl);

R^7 is hydrogen;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

5. A compound of formula (II):



(II)

wherein a, b, A, B and D are as defined in claim 1;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

6. A compound according to claim 5 wherein:

A is -CO-, -C(O)O- or -CONH-;

a is 2 or 3;

B is -CO-, -NHCO-, -CONH or a single direct bond;

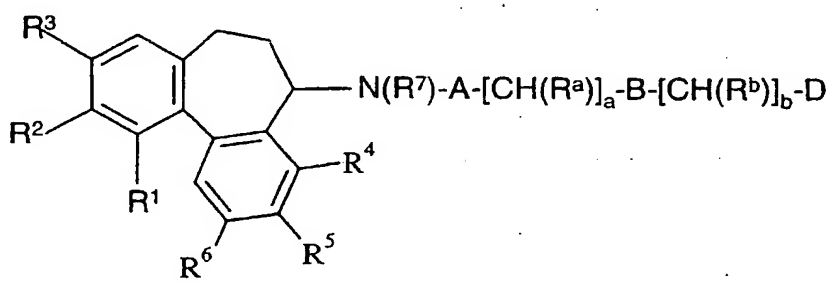
b is 0 or 1;

D is carboxy, phosphoryloxy, hydroxy, amino, N-C_{1-4} alkylamino, N,N-di(C_{1-4} alkyl)amino or of the formula $-Y^1(CH_2)_cR^{11}$ (wherein Y^1 is -NHC(O)- or -C(O)NH-; c is 1 or 2; R^{11} is piperazinyl, morpholinyl or piperidinyl, each of which is linked via a ring nitrogen atom and each ring is optionally substituted by 1 or 2 substituents selected from:

C_{1-4}alkyl, C_{2-4}alkanoyl, carbamoyl, cyanoC_{1-3}alkyl, hydroxyC_{1-3}alkyl, carboxyC_{1-3}alkyl and aminoC_{1-3}alkyl);

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

7. A compound of formula (III):



(III)

wherein:

R^1, R^2 and R^3 are each independently hydroxy, phosphoryloxy (-OPO_3H_2), C_{1-4}alkoxy or an in vivo hydrolysable ester of hydroxy, with the proviso that at least 2 of R^1, R^2 and R^3 are C_{1-4}alkoxy;

A is - CO-, -C(O)O-, -$CON(R^8)$-, -SO_2- or -$SO_2N(R^8)$- (wherein R^8 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, aminoC_{2-3}alkyl or hydroxyC_{2-3}alkyl);

a is an integer from 1 to 4 inclusive;

R^a and R^b are independently selected from hydrogen, hydroxy and amino;

B is -O-, -CO-, -$N(R^9)$CO-, -$CON(R^9)$ -, -C(O)O-, -$N(R^9)$ -, - $N(R^9)$C(O)O-, -$N(R^9)CON(R^{10})$-, -$N(R^9)SO_2$-, -$SO_2N(R^9)$- or a direct single bond (wherein R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, aminoC_{2-3}alkyl and hydroxyC_{2-3}alkyl);

b is 0 or an integer from 1 to 4 inclusive;

D is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) containing 1 or 2 ring heteroatoms, selected independently from O and N, which heterocyclic group may bear 1 or 2 substituents selected from:

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{2-4}alkanoyl, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-di-(C_{1-4}alkyl)carbamoyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, cyanoC_{1-3}alkyl, carbamoylC_{1-3}alkyl, carboxyC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, di-N,N-(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and R^{14} (wherein R^{14} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) containing 1 or 2 ring heteroatoms, selected independently from O and N, which heterocyclic group is optionally substituted by 1 or 2 substituents selected from:

oxo, hydroxy, halogeno, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

R^5 is C_{1-4}alkoxy;

R^4 and R^6 are each independently selected from:

hydrogen, halogeno, nitro, amino, N-C_{1-4}alkylamino, N,N-di-(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy and C_{1-4}alkyl;

R^7 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, aminoC_{1-3}alkyl or hydroxyC_{1-3}alkyl;

or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

8. A compound according to claim 7 wherein:

R^1 , R^2, and R^3 are all C_{1-4}alkoxy;

R^4 and R^6 are independently selected from hydrogen, hydroxy, C_{1-3} alkoxy, and C_{1-3}alkyl;

R^5 is methoxy;

A is -CO-, -C(O)O- or -CONH-;

a is 1, 2 or 3;

B is -CO-, -NHCO-, -CONH, -C(O)O-, -NH-, -NHC(O)O-, NHCONH- or a single direct bond;

b is 0, 1 or 2;

D is piperazinyl or morpholinyl or piperidinyl, each ring being optionally substituted by 1 or 2 substituents selected from C_{1-4}alkyl, C_{2-4}alkanoyl, carbamoyl, cyanoC_{1-3}alkyl, hydroxyC_{1-3}alkyl, carboxyC_{1-3}alkyl and aminoC_{1-3}alkyl;

R^7 is hydrogen;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

9. A compound according to claim 7 wherein:

R^1 , R^2, and R^3 are all methoxy;

R^4 and R^6 are independently selected from hydrogen, hydroxy, methoxy and methyl;

R^5 is methoxy;

A is -CO-, -C(O)O- or -CONH-;

a is 2 or 3;

B is -CO-, -NHCO-, -CONH or a single direct bond;

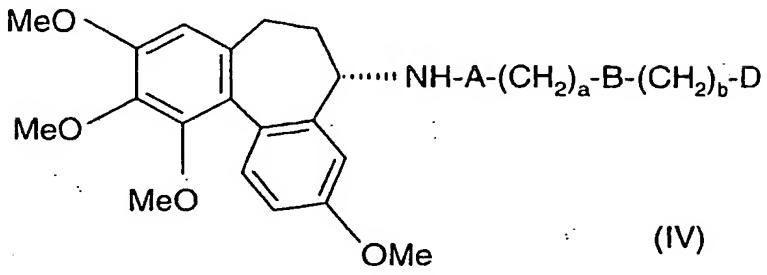
b is 0 or 1;

D is piperazino or morpholino, each ring being optionally substituted by 1 or 2 substituents selected from methyl, ethyl, acetyl, propionyl, carbamoyl and 2-hydroxyethyl;

R^7 is hydrogen;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

10. A compound according to claim 7 wherein:



(IV)

wherein a, b, A, B and D are as hereinabove defined in claim 7;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

11. A compound according to claim 10 wherein:

A is -CO-, -C(O)O- or -CONH-;

a is 2 or 3;

B is -CO-, -NHCO-, -CONH or a single direct bond;

b is 0 or 1;

D is piperazino or morpholino, each ring being optionally substituted by 1 or 2 substituents selected from methyl, ethyl, acetyl, propionyl, carbamoyl and 2-hydroxyethyl;

or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

12. A compound according to claim 10 wherein:

A is -CO-, -C(O)O- or -CONH-;

a is 2 or 3;

B is -CO-, -NHCO-, -CONH or a single direct bond;

b is 0 or 1;

D is morpholino, 4-methylpiperazin-1-yl or 4-acetylpiperazin-1-yl;

or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

13. A compound selected from:

N-[(5S) -3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]-2-[2-aminoacetylamino]acetamide;

4-oxo-4-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]amino]butyl disodium phosphate;

N-{N-[2-(imidazol-1-yl)ethyl]carbamoyl}-5(S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-ylamine; and

2-{N-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]carbamoyloxy}ethyl disodium phosphate;

2-morpholinoethyl *N*-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo [a,c]cyclohepten-5-yl]carbamate;

3-(1-methylpiperazin-4-yl)propyl N-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo [a,c]cyclohepten-5-yl] carbamate;

N-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]-2-[2-aminoacetylamino]acetamide;

2-(1-acetylpiperazin-4-yl)ethyl-N-[(5S)-3,9,10,11-tetramethoxy-6-7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl] carbamate;

N-[(5S)-3,9,10,11-tetramethoxy-6-7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]-4-(1-methylpiperazin-4-yl)-4-oxobutan-l-amide;

4-oxo-4-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]amino]butyl disodium phosphate;

N-{N-[2-(imidazol-1-yl)ethyl]carbamoyl}-5(S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-ylamine;

3-(1-acetylpiperazin-4-yl) propyl-N-[(5S)-3,9,10,11-tetramethoxy-6-7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]carbamate;

N-l-[(5S)-3,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]carbamoyloxy]ethyl disodiumphosphate;

4-morpholino-4-oxobutyl-N-[(5S)-3,9,10, 11-tetramethoxy-6,7-dihydro-5H-dibenzo [a-c]cyclohepten-5-yl]carbamate; and

4-(1-methylpiperazin-4-yl)-4-oxobutyl-N-[(5S)-3,9,10, 11-tetramethoxy-6,7-dihydro-5H-dibenzo[a,c]cylcohepten-5-yl]carbamate;

and pharmaceutically-acceptable salts, solvates or pro-drugs thereof.

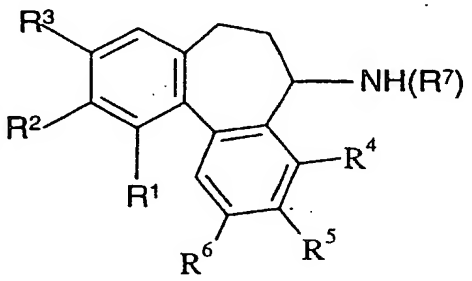
14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt, solvate or pro-drug thereof, in association with a pharmaceutically acceptable carrier.

15. The use of a compound according any one claims 1 to 13, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, in the manufacture of a medicament for use in the production of a vascular damaging effect in a warm-blooded animal.

16. The use of a compound according to any one of claim 1 to 13 or pharmaceutically-acceptable salt, solvate or pro-drug thereof in the manufacture of a medicament for administration in divided doses for use in the production of a vascular damaging effect in a warm-blooded animal.

17. A process for preparing a compound of the formula (I), or a compound of the formula (I) wherein at least 1 functional group is protected, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, B, D, a, b and c are as defined in claim 1, comprising:

a) reacting a compound of the formula (X)



(X)

with a compound of the formula (XI):

$$L^1 - A - [CH(R^a)]_a\text{-}B\text{-}[CH\ R^b)]_b\text{-}D$$

(XI)

wherein L^1 is a leaving group; or

b) converting one compound of the formula (I) into another compound of the formula (I);

c) when a phosphoryloxy group is desired, reacting the corresponding hydroxy compound with a phosphoramidite;

wherein any functional groups are optionally protected.

and thereafter if necessary:

i) converting a compound of formula (I) into another compound of formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate or pro-drug thereof.